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Disease-a-Month

Multiple Myeloma

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Multiple Myeloma

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MULTIPLE MYELOMA is a malignant disease arising from neoplastic proliferation of plasma cell precursors derived from the reticuloendothelial tissues. While myelomatous changes are mainly associated with the bone marrow cavity, solitary tumors (plasmacytomas) may arise in practically any region in the body; and infiltration of the spleen, liver, kidneys and lymph nodes with myeloma cells is a common postmortem finding.

The cause of myeloma is unknown. Unlike leukemia, there is no evidence that radiation or chemical agents play a role in causing this disease. Because of the association of plasmacytosis and the abnormal production of various antibody-like globulins in the plasma, it has been postulated that bacterial or viral agents may be implicated. However, except in mice, evidence that the disease is related to an infectious origin has not been forthcoming.

INCIDENCE

Considered a rare disease 20 years ago, multiple myeloma has been observed much more commonly in recent years. Whether

myeloma has actually increased in incidence, or whether the diagnosis is made more frequently owing to better laboratory technics, is not apparent, and accurate figures are not available. In our clinic, we see 1 case of myeloma to about 6 cases of leukemia in adults. This would mean an estimated rate of about 1 per 100,000 living people, but such figures may be misleading. A more realistic approach is that of MacMahon and Clark (21) as quoted by Osserman (23). These investigators "calculated the cumulative risk that the disease would develop by seventy years of age to be somewhat in excess of 1 per 1,000." In view of a steadily rising population of older individuals in our society, an increasing number of myeloma cases should be expected.

AGE AND SEX

Myeloma is a disease of older age groups; it is seldom found earlier than the fourth decade. In our series of 81 cases, over 90% of the patients were between the ages of 45 and 70 years; the average age was 65. The disease is reported to occur more

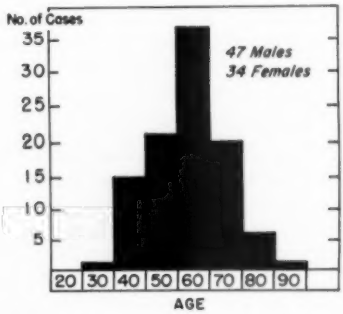

FIG. 1.—Distribution by age and sex in 81 cases of myeloma.

often in males than in females; in our cases, the ratio was 1.4:1 (Fig. 1). MacMahon and Clark (21) found that myeloma was more prevalent in the Negro, compared with the white race, and developed at an earlier age. Our patients included comparatively few Negroes, and the material is too limited to confirm or deny the above observation.

CLINICAL FEATURES

Symptoms

As in many neoplastic disorders, the clinical picture of myeloma varies with the stage of the disease. Before overt manifestations develop, discovery of changes in the serum proteins and the presence of abnormal plasma cell populations in the bone marrow may herald the presence of an early preclinical phase of myeloma. Indeed, Osserman and his associates (23, 25) indicate that primary amyloidosis represents one end of a spectrum of dysproteinemias which has, for the other extreme, the malignant disorder, myeloma. In recent years, with more widespread hospitalization, osteolytic lesions may be found on chest x-ray; or the disease may be suspected because of the discovery of a rapid sedimentation rate, rouleau formation, unexplained anemia or proteinurea on routine laboratory examinations. With the use of bone marrow aspiration and the now widely employed paper electrophoresis of serum, the diagnosis of myeloma usually can be confirmed with little difficulty.

The onset and early course of myeloma are frequently insidious and marked by progressive weakness, anorexia, weight loss and, at times, nausea and vomiting. The common occurrence of gastrointestinal disturbances is not stressed sufficiently in the literature. Complaints of this sort were found in 65% of our patients (see Table 1). Since the gastrointestinal tract is rarely

TABLE 1.—Important Clinical and Laboratory Findings in 81 Cases of Multiple Myeloma (in Per Cent)

Pain	75
Weight loss	65
Anorexia, nausea, vomiting	36
Palpable spleen	16
Palpable liver	23.5
Lesions of the central nervous system	16
Anemia	90
Elevated sedimentation rate	86
Abnormal total plasma proteins and albumin-globulin ratio	61.5
Proteinuria	70
Bence-Jones proteinuria	31
Elevated nonprotein nitrogen	38.5
Osteolytic lesions	68
Pathologic fractures	51
Osteoporosis	43.5

found to be infiltrated with myeloma cells, the anorexia has been ascribed to toxic effects from breakdown products of the myeloma cell. However, it seems more reasonable to attribute the systemic and debilitating effects to the abnormal metabolic demands of the proliferating myeloma cells. Anemia nearly always develops in myeloma, and symptoms due to anemia may be among the outstanding complaints. In the later stages of myeloma, renal involvement and infections serve to intensify the anemia and gastrointestinal complaints. Pain, often intense and requiring narcotics, is a common and outstanding feature of myeloma. It may be of several varieties: severe pain due to expansion of myelomatous tissue in the bone marrow; root pain caused by compression or invasion of the nerve roots, the pain of pathologic fractures and occasionally periarticular pain simulating arthritis. Back pain due to myeloma involving the vertebrae usually is a result of pathologic fracture of the lower spine. This type of pain is made worse by turning or twisting and is aggravated by coughing or sneezing; indeed, even pressure of the hand on the bed may cause a severe paroxysm of pain.

Physical Findings

Physical findings in myeloma are of the nonspecific type. Pallor and evidence of weight loss are usually present, and hepatomegaly may be found in 10–25% of patients. Infiltrative lesions of the skin and obvious tumor masses are uncommon but, when present, are particularly important as sites available for diagnostic aspiration or biopsy. The presence of plasmacytomas has been reported by a number of observers, the incidence varying from 5 to 25% of cases (1, 4, 10, 45). In our series there were 6 palpable tumor masses in 81 patients.

Physical changes secondary to protein abnormalities include those found with amyloidosis, such as macroglossia, skin papules and nodules, purpura and alopecia. The presence of cryoglobulinemia may give rise to local capillary damage, resulting in ecchymoses and purpura. Cold-precipitable globulins may also cause Raynaud's syndrome, ulceration and necrosis of the skin and cold urticaria.

NEUROLOGIC ASPECTS

Involvement of the nervous system is relatively common in myeloma and may be brought about by several mechanisms. Compression of the spinal cord or nerve roots may occur by direct pressure of a plasmacytoma or by infiltration of perineural structures. Occlusion of vascular supply may result in serious impairment of motor and sensory function. One of the most dramatic complications is the sudden compression of the spinal cord by plasmacytoma, resulting in paralysis of the lower extremities and the urinary bladder. In our series, there were 2 such cases, and both patients were promptly treated by decompression of the spinal cord, followed by local x-ray therapy. This resulted in a prolonged and complete recovery in one of the patients; in the other, motor function was restored but residual bladder paralysis persisted. At times, a more slowly progressive cord involvement may occur. This was found in 2 of our cases. Surgical intervention was not necessary; one patient responded to urethan, while in the other, the process was arrested by a combination of local x-ray and urethan. The patient treated with urethan alone had the interesting finding of a myeloma protein in the spinal fluid, demonstrated by paper electrophoresis. This protein, as well as an abnormal globulin in the urine, disappeared following urethan therapy. Collapse of vertebrae due to pathologic fractures may give rise to cord or nerve root compression, resulting in sensory and motor disturbances. Depending on the extent of the compression, these lesions may result in a great variety of neurologic complaints. Neural involvement has also been described as due to infiltration or compression of nerve roots or peripheral nerves by para-amyloid deposits.

Recently emphasis has been placed on the occurrence in myeloma of a nonspecific polyneuropathy. This has been carefully described by Victor and his co-workers (43), and it occurred in 3 of our patients. As Osserman (24) has pointed out, this neuropathy is of obscure origin and is similar to the polyneuropathy associated with other malignant tumors.

In our series, there were 3 cases in which unexplained cerebral manifestations occurred. These consisted of confusion, disorientation and clouded sensorium. These complaints could not be ex-

plained by uremia, electrolytic changes or direct involvement of the central nervous system by myeloma. All 3 cases were first seen during the terminal stage of the disease. Whether some systemic "toxic" factor analogous to that described for peripheral neuropathy can be implicated is a matter of speculation. It is of interest to note that one manifestation of central nervous system involvement, "coma paraproteinemicum," may result from the impair-

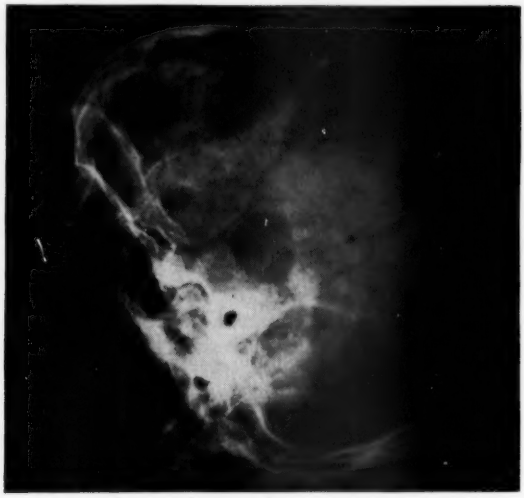

FIG. 2.—Osteolytic lesions in the skull due to myeloma.

ment of the cerebral circulation due to increased serum viscosity caused by macroglobulins. Two of our patients showed positive reactions to water dilution tests* for these abnormal proteins of high molecular weight, but other confirmatory studies were not carried out in these patients.

ROENTGENOLOGIC BONE CHANGES

Changes in bone are among the most frequent findings in myeloma; and eventually osseous lesions, demonstrable by x-ray,

*A practical test is performed by allowing a large drop of serum to fall into a beaker of distilled water. A positive reaction is indicated by a dense white cloudlike flocculation. The reaction is positive in most, but not all, cases of macroglobulinemia.

develop in 90% of the patients. The classic x-ray picture is that of punched-out, radiolucent osteolytic lesions varying in size from a few millimeters to several centimeters in diameter. At times these lesions may reach large proportions and erode through the

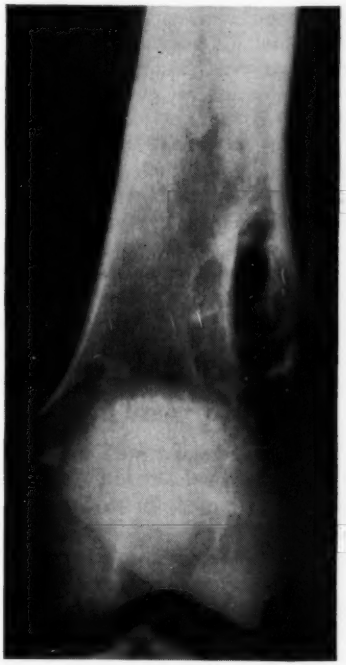

FIG. 3.—A large osteolytic lesion in the femur in a patient with multiple plasmacytomas.

cortex of the bone. Characteristically, there is little or no osteoblastic reaction (Figs. 2 and 3).

The destructive lesions are usually multiple and most often are found in the skull, vertebrae, ribs, pelvis and long bones. While highly suggestive of myeloma, similar osteolytic lesions may occur with metastatic cancer and other tumors. While the disease may

appear as a solitary lesion, almost invariably multiple areas become involved. Solitary myelomas have been described in the literature; but in most instances, patients with such lesions will be found to have disseminated disease if followed long enough. In our series, 2 cases of multiple plasmacytomas have been followed for years without evidence of systemic involvement, such as abnormal plasma proteins, anemia or diffuse infiltration of the marrow with myeloma cells. Snapper and his associates (42) point out that such cases are rare clinical entities.

Diffuse osteoporosis is the most commonly encountered bone abnormality in multiple myeloma. It is often overlooked or attributed to other conditions, such as aging, postmenopausal changes or other metabolic conditions.

Pathologic fractures are well-known complications associated with obvious bone destruction. They occur most frequently in the vertebrae, ribs and long bones. In our series, 50% of the patients developed pathologic fractures. In fracture sites with no overt evidence of an osteolytic process, bone infiltration not demonstrable by x-ray is the underlying pathologic lesion.

RENAL DISEASE

Renal disease is often associated with multiple myeloma. Proteinuria occurs in 60–90% of the cases (4, 5, 6, 42), and uremia is frequently the terminal event in this disease. The so-called "myeloma kidney" is the classic example of renal damage; but infection in the urinary tract, nephrosclerosis, calculi and renal calcinosis may contribute, in varying degrees, to ultimate renal failure. The actual incidence of myeloma kidney is not well established, and in many large series of cases no figures are available. In our 36 autopsied cases, myeloma kidney was found in 15 patients. Amyloid deposits may occur in the kidney and cause a nephrotic syndrome; however, amyloidosis is not an important contributing factor in uremia (42).

In the myeloma kidney, the renal damage is attributed to deposition of an abnormal globulin of small molecular weight as droplets in the cytoplasm of tubular epithelium and as casts in the renal tubules. These casts may present a laminated appearance and are often surrounded by multinucleated giant cells. The

giant cells are considered by some to be a syncytium of tubular epithelium and by others to be foreign-body giant cells. As the process develops, the tubular epithelium degenerates, resulting in thinning of the tubular wall with dilatation and tortuosity. Finally, complete replacement of the nephron by fibrous tissue results. The glomeruli apparently escape obvious damage; however, recent studies in a series of 16 cases (17) indicate that, unrelated to the presence of myeloma kidney, thickening of the basement membrane may be found.

Various studies (2, 11, 22) have been carried out on renal function in myeloma, and most of these indicate impairment of both tubules and glomeruli. However, in this disease there are many factors which may impair renal function other than the specific damage inflicted by proteinuria. The stage of the disease, the presence of anemia, increased blood viscosity, infections and hypercalcemia must be taken into account when renal function is evaluated in myeloma patients. It should also be pointed out that the presence of Bence-Jones protein does not invariably result in renal damage. Osserman (24) notes that this may reflect the differences in the physicochemical properties of these abnormal proteins.

As noted above, uremia is often a frequent complication in myeloma. The clinical and biochemical manifestations are similar to those of uremia from other causes except that hypertension is seldom present. In our experience, when uremia develops in association with myeloma kidney the condition is irreversible and the course is usually steadily and rather rapidly downhill. As a practical point, it should be emphasized that patients with myeloma may not tolerate intravenous pyelography. Various investigators (28) have pointed out that this procedure, employed in the study of proteinuria of unknown origin, has resulted in renal failure and death in some patients who were subsequently found to have myeloma at autopsy.

LABORATORY FINDINGS

While symptomatology and physical findings are nonspecific, the unique characteristics of many laboratory findings in myeloma are of special diagnostic significance.

Peripheral Blood

Some degree of anemia develops in practically every case of myeloma. The anemia is normocytic and normochromic. However, macrocytosis may be present, but it is usually not associated with marked anisocytosis or poikilocytosis. With extensive replacement of the marrow by myeloma cells, the anemia may be severe and refractory to all therapy. Poorly defined hemolytic mechanisms, renal disease and infections may also contribute to the development of anemia in myeloma patients.

Marked rouleau formation and clumping of red cells are characteristics frequently noted on peripheral blood and bone marrow smears. Pseudoagglutination may be so marked that at times it may interfere with blood grouping and cross-matching. An exceptionally rapid erythrocyte sedimentation rate is a common phenomenon and may be observed at the bedside during the collection of blood in the syringe and specimen tubes.

Leukocytes and platelets are usually unremarkable, although leukopenia and thrombocytopenia may occur in the advanced stages of the disease or develop as a result of therapy. On scanning blood smears, a small number of plasma cells may be discovered. More rarely, considerable numbers of myeloma cells may appear in the peripheral blood. In our series, 4 patients showed from 4 to 10% plasma cells; and in 1 case, classified as plasma cell leukemia, there was marked leukocytosis of 77,000 white cells and most of the cells were of the immature plasma cell variety.

Bone Marrow

Marrow aspiration is the most important single diagnostic procedure in myeloma. Specimens obtained from the sternum, iliac crests or vertebral spinous processes provided cytologic proof of myeloma in the vast majority of suspected cases. Because of the patchy nature of the disease, marrow aspiration may result in a dry tap or a specimen inadequate for diagnosis. In such instances, repeated marrow aspirations from various sites, or actual marrow biopsy, may be necessary to provide an adequate specimen. With multiple plasmacytomas, the general marrow may not

show infiltration with myeloma cells. However, direct aspiration or biopsy of an isolated lesion will provide material for a histologic diagnosis. In the typical case, marrow smears reveal sheets of myeloma cells and reduction of other marrow elements. Marked rouleau formation and a peculiar bluish background, due to the abnormal plasma protein, are frequently features of the preparation. The myeloma cell population may be a uniform type of adult-appearing plasma cells, but marrow populations in other cases may show a collection of extremely primitive plasmablasts. These cells are frequently bizarre in appearance, usually containing a large nucleus with loosely arranged chromatin and a large distinct nucleolus. The cytoplasm is abundant and has a peculiar dense blue appearance, with at times pseudopodia-like projections. Vacuoles, Russell bodies or grape cells,* or other cytoplasmic inclusions may be present. Even in these primitive cells the characteristics of the eccentrically placed nucleus may be retained.

The myeloma cell type may vary considerably in appearance from case to case. All gradations from the huge plasmablasts to intermediate proplasmacyte and adult-appearing plasma cells may be encountered. Often a pleomorphic picture may be present with a mixture of adult and more primitive myeloma cells. The number of myeloma cells may range from 2 to 90%. Even with small numbers of very immature myeloma cells in a scanty preparation, the diagnosis of myeloma should be strongly suspected. In such instances, additional confirmatory evidence, either cytologic or biochemical, should be obtained before a definite diagnosis is established. A source of diagnostic difficulty may be the association of hyperglobulinemia with the presence of increased numbers of plasma cells in the bone marrow. As pointed out by Osserman and his associates (23, 25), conditions such as primary amyloidosis may indeed represent transitional stages from benign plasmacytosis to the neoplastic disease myeloma. The plasma cells in the marrow may represent up to 60% of the cellular elements in disorders such as cirrhosis of the liver, subacute bacterial endocarditis, agranulocytosis, collagen disease, carcinomatosis, tuber-

*Russell bodies are cytoplasmic inclusions in abnormal plasma cells. With Wright or Giemsa stain, they appear as large, round or oval bodies and usually stain red. Grape cells are abnormal plasma cells containing colorless or bluish vacuole-like cytoplasmic bodies; sometimes they completely fill the cytoplasm. The presence of Russell bodies or grape cells is not pathognomonic of myeloma type plasma cells.

culosis and rheumatoid arthritis (27). The cells may be multinucleated and at times will contain vacuoles or Russell bodies. However, they rarely demonstrate the very immature and bizarre features of plasmablasts often noted in cases of myeloma. Without evidence of osteolytic lesions, Bence-Jones proteinuria or typical globulin peaks on paper electrophoresis of the plasma, it may be impossible to make a definitive diagnosis in a small percentage of cases. Under these circumstances, radiation and chemotherapy should be withheld in favor of a policy of watchful waiting.

Calcium

In view of the widespread involvement of bone, it is not surprising that elevated serum calcium levels are frequently present in myeloma patients. In various reports the incidence of hypercalcemia ranges from 20 to 50% (1, 4, 44). In 2 of our cases, serum calcium was 18.8 and 20.4 mg./100 ml., respectively, and both patients had hypercalciuria. Renal function may be impaired by the deposition of calcium in the tubular epithelium. While usually reversible by the administration of fluids and corticosteroids, renal damage may be progressive. At times, grossly visible deposits of calcium are noted in the kidney at autopsy.

Phosphorus

Usually, serum phosphorus levels are normal or slightly elevated; but in the presence of long-standing renal disease and uremia, serum phosphorus may be markedly elevated.

Alkaline Phosphatase

As a rule, serum alkaline phosphatase activity is normal or only slightly elevated in myeloma. The lack of an elevated alkaline phosphatase in the presence of hypercalcemia and hypophosphatemia is helpful in the differential diagnosis between hyperparathyroidism and myeloma.

Uric Acid

Elevation of serum uric acid is a very common finding in myeloma. In our series, markedly increased serum uric acid levels were noted in the absence of renal disease. As in myelogenous leukemia and other conditions in which there is rapid proliferation and breakdown of neoplastic cells, hyperuricemia is related to the characteristic acceleration of nucleic acid metabolism. However, as emphasized by Osserman (24), despite the often greatly elevated uric acid levels, gout is an uncommon complication in myeloma patients.

ABNORMAL PROTEIN METABOLISM

In myeloma the unique protein metabolism offers a challenging opportunity to investigate fundamental mechanisms of antibody formation and the role of specific cells in protein synthesis. Studies in this field also afford the intriguing possibility of correlating a spectrum of dysproteinemic states from benign plasma cell hyperactivity to neoplastic proliferation. Historically, clinical interest in myeloma proteins developed because of the peculiar laboratory characteristics which provided valuable diagnostic clues to this disease. Of more basic interest is the concept that abnormal protein may produce tissue damage by auto-immune or physicochemical reactions. It is already well established that dysproteinemia can produce vascular damage, disturbances in the coagulation mechanism (6, 14, 15), decreased antibody synthesis (20, 45), renal damage and a variety of symptoms and signs arising from para-amyloid deposits.

The protein abnormalities in myeloma may be discussed under three headings—abnormal serum proteins, excretion of Bence-Jones protein in the urine and para-amyloidosis. Production of abnormal serum proteins and Bence-Jones protein has been considered a function of abnormal plasma cells. Putnam and his co-workers (25, 29, 34, 35, 36) have shown that these proteins are heterologous and that each patient makes an individually specific abnormal protein. The evidence for production of abnormal proteins by plasma cells is largely indirect and based on the decrease of abnormal serum and urine proteins following urethan

therapy (8, 38) and the removal of a large solitary plasmacytoma (37). Recently, immunohistochemical and immunoelectrophoretic methods have demonstrated the presence of abnormal protein in the myeloma cell (39).

Many other aspects of protein synthesis in myeloma have been clarified by the work of Putnam and his associates. Using isotopic technics, these investigators were able to show that myeloma proteins are not breakdown products of tissue protein but are synthesized directly from the circulating nitrogen pool (13, 25, 29, 30, 32). Recent evidence also favors the concept that Bence-Jones protein is not split off from large protein molecules but may be synthesized in the plasma cell as a precursor in the formation of abnormal plasma globulins (25, 29, 30, 31). While rare in occurrence, abnormal homogeneous plasma globulins may be found in patients with carcinoma, malignant lymphomas and a few other diseases; the "peaks" found on paper electrophoresis are not pathognomic for myeloma (3, 26). However, in regard to Bence-Jones proteinuria, the consensus is that this abnormal protein of low molecular weight is excreted only in cases of multiple myeloma.

Serum Proteins

Increased total serum protein has long been recognized as a feature of multiple myeloma and, when determined by quantitative methods, has been reported in 50–70% of cases (1, 4, 42). Nevertheless, it is well known that abnormal serum globulins may be present even when the total protein is not elevated. Marked increase in the total serum protein and gamma globulin may be found in a variety of diseases, including cirrhosis, collagen diseases, chronic infections and neoplasms. However, the typical globulin band noted on electrophoresis occurs almost exclusively in myeloma, macroglobulinemia and rare cases of malignant lymphoma.

The study of serum proteins by the easily available method of paper electrophoresis has contributed greatly to earlier and more accurate diagnosis of myeloma. The abnormal protein appears as a dense, narrow homogeneous band, most often in the early gamma globulin zone (Fig. 4). Less frequently, peaks appear between the gamma and beta zones and in the beta globulin

fraction. Rarely will abnormal peaks be found in the alpha globulin zones. Characteristic peaks of abnormal protein are found in 70–80% of myeloma patients when paper electrophoresis is employed. With more sensitive methods, such as the Tiselius technic and starch electrophoresis, practically all myeloma patients will be found to have abnormal protein in the serum. Although the electrophoretic mobility of the myeloma protein varies from patient to patient, in the individual patient it remains constant throughout the course of the disease. As the disease

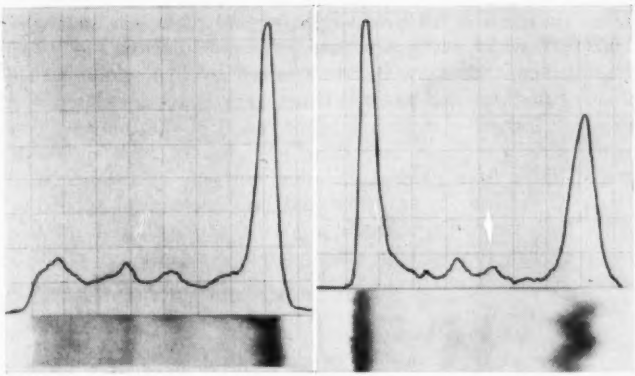

FIG. 4.—Paper electrophoretic patterns of normal and of myeloma serum. *Left*, normal pattern. *Right*, typical pattern in multiple myeloma with a slow-moving gamma peak.

progresses, myeloma globulin tends to increase while albumin decreases, unless influenced by treatment. In the advanced stage of the disease, abnormal globulin may constitute 70% of the total serum protein.

Extensive studies have been carried out on the immunologic characteristics of myeloma proteins and macroglobulins (8, 40, 41). These investigations indicate that myeloma proteins of the gamma globulin type are closely related to normal gamma globulin. However, Putnam and his co-workers point out that myeloma globulins are specific for each patient and that they are immunologically distinct from each other and from normal gamma globulins (25, 29, 36). Macroglobulins possess similar

individuality, and they share antigenic specificity and other characteristics with myeloma proteins.

Investigation of the physical properties of myeloma proteins, employing ultracentrifugal methods, has shown that these globulins have sedimentation constants of 6–7 Svedberg units which correspond to a molecular weight of 160,000. These values are similar to normal gamma globulins. Occasionally, globulins of a higher molecular weight are detected in the beta globulin type of myeloma protein. Ultracentrifugation studies have been of the greatest value in the detection of macroglobulins (with sedimentation constants of 19 Svedberg units and molecular weight of 1,000,000) which occur in primary hyperglobulinemia (44). This dysproteinemic disorder is characterized by hyperglobulinemia, bleeding diathesis and anemia. However, it is not associated with osteolytic lesions or myeloma cell invasion of the marrow. Putnam's studies indicate that these globulins of high molecular weight differ from gamma globulins not only in sedimentation constants but also in antigenic and physicochemical properties. While high serum viscosity and a positive water dilution reaction are frequently present with macroglobulinemia, the use of ultracentrifugal or immunologic methods are necessary to establish a diagnosis (29).

Among the important contributions to an understanding of the nature of the abnormal myeloma proteins have been the studies of Putnam and his associates on the amino acid composition of the terminal nitrogen groups of myeloma globulins (9, 12, 33, 41). This research reveals that normal gamma globulin and myeloma proteins have, for the most part, identical chemical structures. However, differences are found in the presence or absence of amino acids in the terminal nitrogen position and other loci. Putnam points out that these differences in amino acid composition account for the electrophoretic, structural and antigenic individuality of myeloma proteins.

Cryoglobulinemia

A peculiar feature of some abnormal myeloma proteins and macroglobulins is their capacity, on cooling, to form a firm gel or flocculent precipitate. When the serum is warmed, the gel or

precipitate disappears. Varying amounts of cold-precipitable globulin may be found in a large number of disorders associated with increased serum gamma globulin. However, the presence of large amounts of cryoglobulin is nearly always indicative of myeloma, macroglobulinemia or lymphosarcoma. In 6 of our 81 cases of myeloma, there was marked cryoglobulinemia. The clinical significance of cryoglobulins arises from vascular damage due to precipitation of protein in small vessels. Purpura, ecchymoses, Raynaud's syndrome, urticaria and the more serious sequelae of vascular occlusion may follow exposure to cold in patients with cryoglobulinemia.

Hemorrhagic Disorders

A variety of hemorrhagic manifestations have been reported in myeloma, and bleeding occurred in 10% of our cases. Bleeding tendencies have consisted mainly of nosebleeds, bleeding into the skin and bleeding from the gums, as well as gastrointestinal and genitourinary tract hemorrhage. In addition to capillary damage due to increased serum viscosity, the abnormal globulins apparently interfere with the clotting factors by protein binding or complexing. Coagulation defects caused by the inhibition of factor V and factor VII, prothrombin, fibrinogen and possibly calcium have been ascribed to the action of myeloma proteins and macroglobulins (6, 14, 15).

Bence-Jones Proteins

The classic test for Bence-Jones proteinuria based on thermal solubility has proved to be of limited value. A more practical method for the detection of abnormal globulins in the urine is to employ the simple screening test suggested by Snapper (42). This consists of layering the urine over concentrated hydrochloric acid. If a white ring does not form, Bence-Jones proteins are not present. If the test shows proteinuria, paper electrophoresis is carried out, either on the unconcentrated urine, if proteinuria is marked, or following dialysis, if little protein is present. Even in the presence of albumin or other nonspecific proteins, homo-

geneous components migrating in the globulin region, which are practically pathognomonic for myeloma, can be readily identified. The combined use of urine and serum electrophoresis will detect diagnostically significant abnormal proteins in over 90% of myeloma patients.

The physical and chemical aspects of Bence-Jones proteins have been investigated by Putnam (34). He states that these proteins have sedimentation constants of about 3–4 Svedberg units and molecular weights averaging about 44,000. Owing to their low molecular weight, Bence-Jones proteins are rapidly excreted and cannot be identified in the serum by ordinary electrophoretic technics. Other studies demonstrate that these proteins are related to normal gamma globulins, but even more closely to homologous myeloma globulin (7, 19). Isotopic studies with labeled amino acids demonstrate that Bence-Jones proteins are not formed by renal cleavage of myeloma globulins (25, 29, 30, 31). Bence-Jones proteins apparently are synthesized from the free amino acid pool; and experiments, according to Putnam, suggest, but do not prove, that these proteins may be manufactured in the plasma cells as a precursor of abnormal myeloma globulins.

Para-amyloidosis

The classification, chemical composition and pathogenesis of amyloid deposits in various tissues are still matters of controversy. However, Osserman (24), in his excellent discussion of tissue proteinosis, points out that recent investigations have contributed a great deal to our understanding of the nature and possible origin of these unique tissue infiltrates.

Secondary amyloid, the type found in association with long-standing suppurative diseases, tuberculosis and other chronic disorders, has been shown to be very similar, by chemical analysis and other studies, to amyloid produced experimentally by hyperimmunization in animals. Typically, these infiltrates involve the liver, spleen, lymph nodes, kidneys and adrenals. Secondary amyloid displays metachromatic staining properties and has an affinity for Congo red. This material is apparently elaborated by plasma cells derived from the reticuloendothelial system of

parenchymal organs and lymph nodes. The cytoplasmic ribonucleoprotein undergoes transformation to a glycoprotein (stains with periodic acid Schiff reagent) and, as the cells degenerate, forms extracellular amorphous eosinophilic aggregates. Osserman (24) indicated that the synthesis of amyloid plasma cells is analogous to the production of gamma globulin; in fact, amyloid has been found to be chemically and immunologically related to gamma globulin.

In approximately 10% of myeloma patients, para-amyloid (primary amyloid) deposits are found in tissues. Characteristically, these infiltrates involve the tongue, gastrointestinal tract, heart and blood vessels, skin, periarticular tissues and nerves. The primary or para-amyloid material is not metachromatic and has little affinity for Congo red.

Osserman's recent studies (24) on 12 cases of primary amyloidosis confirm and extend the earlier observations and theories of Magnus-Levy and Apitz. All of Osserman's cases showed abnormal urinary proteins on paper electrophoresis, and there was an associated bone marrow plasmacytosis. In 6 cases, osseous lesions developed during the course of the disease. The deaths in the remaining 6 cases were attributed to the effects of infiltrates, mainly in the heart. Osserman suggests that the abnormal protein of low molecular weight diffuses through the capillaries into the tissues and that, in sites where there are complementary polysaccharides, protein-carbohydrate binding takes place, resulting in insoluble complexes.

Although all the problems are not completely clarified and there is considerable overlapping in the clinical, pathologic and physicochemical aspects of disorders associated with para-amyloid infiltrates, the hypothesis that primary amyloidosis and multiple myeloma are part of a spectrum of plasma cell dyscrasias is an attractive one.

TREATMENT

Chemotherapy

Multiple myeloma is an inevitably fatal disease uniquely resistant to most forms of treatment. While in a few cases remissions

have been attributed to various alkylating agents, such as mechlorethamine hydrochloride (nitrogen mustard), triethylene melamine, chlorambucil and triethylene thiophosphoramide (thio-TEPA), these compounds, along with folic acid antagonists and antimetabolites, are generally ineffective in the treatment of myeloma.

On the other hand, urethan has been of limited but definite benefit in our experience. During the past 12 years an attempt has been made to treat practically all of our myeloma patients with this drug. Obviously, many patients did not receive an adequate course of urethan because of the advanced stage of the disease, renal insufficiency or intolerance to the drug. It should be pointed out that, even with adequate therapy, little or no beneficial effect has been obtained in the majority of patients. Nonetheless, gratifying remissions have occurred in some of our patients: pain was relieved, appetite, strength and weight regained, and the patients were restored to a normal active existence for varying periods of time. From the laboratory standpoint, anemia improved, striking reduction of abnormal plasma globulins was noted, Bence-Jones proteinuria decreased or disappeared and, in some instances, healing of osteolytic lesions took place.

Unfortunately, urethan therapy causes gastrointestinal disturbances in a high percentage of patients. While enteric-coated tablets may be of some help, they may pass unabsorbed through the gastrointestinal tract. The use of urethan suppositories has been the best means of administering the drug in our experience; but with high dosages, even the rectal route does not prevent gastrointestinal distress. The dose of urethan should be 3–6 Gm. daily, and the dosage should be regulated by the level of the white cells (24). The objective should be to maintain a state of moderate leukopenia—i.e., 2,000–3,000 white cells per cubic millimeter. In about 5% of our patients who were treated with urethan, severe neutropenia developed; however, the leukopenia spontaneously cleared up following cessation of urethan therapy. An adequate trial of therapy consists of 2–6 Gm. of urethan daily for 4–6 weeks. Following the initial period, the dose should be adjusted to maintain a low leukocyte level. It has been our practice to continue the patient indefinitely on a maintenance dose of 1–3 Gm. of urethan daily. One patient with classic multiple

myeloma, including anemia, plasma protein changes and osteolytic lesions, was maintained on a daily dose of urethan for 3 years. During this period he was asymptomatic and carried on full social and business activities. However, he suddenly developed renal failure and soon died.

At times it is difficult to assess the value of urethan in the treatment of myeloma, as the following cases illustrate.

A 46-year-old man suddenly, in 1946, developed paralysis of the lower extremities and the bladder. The spinal cord was decompressed and a tumor removed from the spinal canal; the tumor proved to be a plasmacytoma. The patient subsequently was treated for 2 years with urethan and made a nearly complete recovery; paralysis of the legs cleared up, although he retained some residual bladder paralysis. He was able to return to hard labor, but during the next 10 years he developed huge osteolytic lesions in the ribs, clavicles, iliac crest, ischium, orbit and tibia. During this period, three pathologic fractures occurred, and he was eventually confined to a wheel chair because of nonunion of a tibial fracture. All other osteolytic lesions and pathologic fractures had previously completely healed after intensive x-ray therapy. To date (1960), this man has received over 60,000 r to the various myeloma lesions. No changes in the peripheral blood values, serum proteins or kidney function have been noted. Although many bone marrow aspirations failed to reveal myeloma cells, on one occasion aspiration of an iliac crest mass revealed sheets of rather immature myeloma cells. It is doubtful that urethan played any useful role in this case of multiple plasmacytomas, but the x-ray therapy to local bone lesions was unquestionably of great benefit.

As an example of temporary but very striking remission due to urethan, the following case is presented.

A 57-year-old woman was admitted to the Boston City Hospital in October 1956, with pneumococcal pneumonia and recovered on antibiotic therapy. In November 1957 she was again admitted because of severe back and flank pain. At this time she looked chronically ill, and marked precordial heaving was noted. The patient had a slight lateral nystagmus and the tongue showed left hemiatrophy. X-rays of the chest revealed extensive osteolytic lesions, especially in the ribs, and severe generalized osteoporosis. A bone marrow aspiration showed 80% myeloma cells, and a diagnosis of multiple myeloma was established. The serum proteins were elevated, and paper electrophoresis showed two sharply defined peaks in the gamma region. Paper electrophoresis also showed an abnormal protein, migrating as a gamma globulin, present in both the spinal fluid and urine. Because of urinary retention, a Foley

catheter was inserted. Pyelonephritis developed and the nonprotein nitrogen rose to 108 mg./100 ml. Treatment was started with urethan; and subsequently the severe back pain disappeared, bladder function returned to normal, anemia improved and the abnormal protein disappeared from the urine and spinal fluid. The effect of urethan therapy on the hematocrit, white count and the serum protein level is shown in Figure 5. Over a period of several months the extensive osteolytic lesions recalcified to a marked degree. The patient was able to return

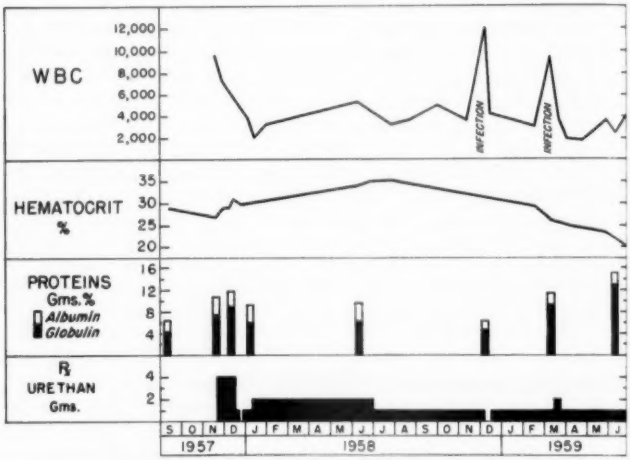

FIG. 5.—Effect of urethan on white cell count, hematocrit and proteins in a patient with multiple myeloma.

to household duties and was followed on an outpatient basis throughout 1958. In December 1958 she was readmitted because of another bout of pneumonia but recovered quite promptly. During the late winter she developed a throat infection, and in March 1959 severe laryngeal edema necessitated an emergency tracheotomy. Although she recovered from this episode, the patient did not do well; and in June 1959 she was readmitted because of anorexia, weight loss, nausea, vomiting and mental deterioration. On this admission the hematocrit was 23, the serum proteins were 15.3 Gm./100 ml., and the reaction to the water dilution test for macroglobulin was positive. She again developed pneumonia, but this time did not respond well to antibiotics. Bleeding from the nose

and mouth began, and she required multiple transfusions to maintain the hematocrit. The blood urea nitrogen rose to 39 mg./100 ml., and the terminal event was massive gastrointestinal hemorrhage. It is possible that the cerebral manifestations and the bleeding were related to the macroglubulinemia.

In our series, 20% of the adequately treated cases of myeloma responded to urethan therapy with excellent remissions. In view of the ineffectiveness of other chemotherapeutic agents and the relatively low incidence of serious toxic reactions, a trial of urethan therapy is indicated in nearly all myeloma patients.

ACTH and Corticosteroids

The use of ACTH and the corticosteroids has been disappointing. In our series, no remissions of the disease could be attributed to corticosteroid therapy. However, in the presence of severe anemia, especially if there is a hemolytic component, corticosteroids may be helpful in reducing the need for blood transfusion. Also, if purpura and bleeding due to thrombocytopenia develops, corticosteroids should be employed to decrease capillary fragility. It should be pointed out that corticosteroids may play a useful role in controlling hypercalcemia. Two of our myeloma patients with very high serum calcium levels and hypercalciuria were greatly benefited by corticosteroid therapy, and in both cases the high serum calcium returned to normal levels after administration of prednisone.

Radiation Therapy

A number of radioactive isotopes have been employed in the treatment of myeloma, including P^{32}, I^{131}, Sr^{89}, Ca^{45} and Y^{90}. However, little success has been achieved with their use, and radioactive isotope therapy is considered of no practical value in myeloma. On the other hand, local x-ray therapy to osteolytic lesions, pathologic fractures and plasmacytic tumors has been of great benefit in many cases. Gratifying relief of pain, recalcification of osteolytic lesions, healing of pathologic fractures and regression of soft-tissue masses have occurred in nearly all cases treated in our series. However, whole-body radiation for dissemi-

nated myeloma is not feasible, and effective x-ray therapy is limited to local lesions.

General Measures

Most patients with myeloma are in the older age groups; and in these patients, demineralization of the bones occurs, not only from the myelomatous process, but as a factor of aging. Since this is especially true if the patient is bedridden, every effort should be made to keep him ambulatory. Casts, back braces and other supportive measures should be utilized, along with intensive local x-ray therapy. Testosterone has been advocated for osteoporosis; but in view of the pathogenesis of demineralization of bone in myeloma patients, it is difficult to visualize a useful role for this hormone.

Infections are notoriously common in patients with myeloma, owing to lack of effective antibody production (10, 45). Prophylactic broad-spectrum antibiotics should be avoided; instead, the infections should be treated, as they arise, with specific antibiotics selected according to sensitivity tests. The use of gamma globulin in this disease is impractical and not warranted.

Anemia due to myelomatous marrow infiltration may respond to urethan therapy. If there is hemolysis, corticosteroids may be helpful; in severe refractory anemia, the ultimate recourse will be to blood transfusion therapy. Blood should be given to alleviate symptoms due to anemia and to maintain the patient in some degree of activity. The question of continuing transfusion therapy to a bedridden patient with far advanced disease is a matter of individual judgment on the part of the attending physician.

DURATION OF DISEASE

The survival time of patients with multiple myeloma is very variable. In our series of 81 patients, only 8 are still alive. As shown in Figure 6, the great majority of the patients died within 2 years of onset of the disease. The mean survival rate of all patients was 25.1 months. If terminal cases and the few patients surviving over 100 months are eliminated, the mean survival rate would be 17.7 months.

In 48 patients who received adequate urethan therapy, the mean survival rate was 30.8 months. If the 4 patients who survived over 100 months are dropped out, the average survival time would be 18.2 months. The median survival rate for all patients was 12.9 months; and for the adequately treated group, median survival time was 15.8 months. Considering the bias in the selection of patients for urethan therapy, there is no evidence from this experience that urethan significantly prolongs the life of myeloma patients.

It is difficult to evaluate the factors which influence the course of myeloma. Patients with a uniform adult plasma cell population

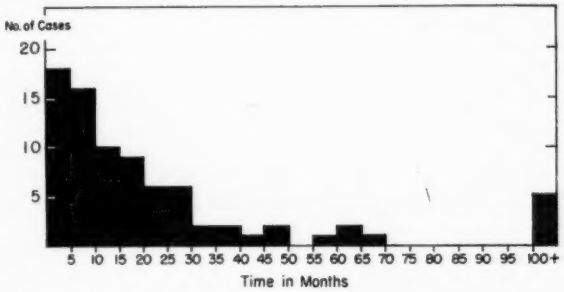

FIG. 6.—Length of survival in 81 cases of multiple myeloma, including 8 living patients.

seem to run a more prolonged course than do those with diffuse marrow infiltration of very immature myeloma cells. However, most patients have a mixed myeloma cell population; and, when associated conditions such as a renal damage, infections and anemia are considered, the impossibility of accurately correlating cell type with length of survival becomes obvious.

SUMMARY

1. Multiple myeloma is an uncommon but uniquely important disease, and it is encountered with increasing frequency.

2. Clinically, the occurrence of pain, especially in the back, unexplained anemia or proteinuria in older people should arouse

suspicion of multiple myeloma. The diagnostic importance of bone changes by x-ray, of marrow aspiration and of use of paper electrophoresis of the serum and urine has been stressed.

3. The treatment of myeloma, in common with that of most neoplastic disorders, is unsatisfactory. However, some patients obtain remissions on urethan, and painful bone lesions are greatly improved by local x-ray therapy.

4. The abnormal protein metabolism in myeloma is a fascinating aspect of this disease and presents fundamental problems concerning the synthesis of globulins in plasma cell dyscrasias. The role of these proteins in the pathogenesis of renal damage and para-amyloidosis has been discussed in the light of newly acquired immunologic and physicochemical knowledge.

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